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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,470	08/16/2001	James M. Hagberg	108172-00071	6361

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,470	HAGBERG ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 4/7/03. Claims 2 and 4 have been amended and claims 1 and 3 have been cancelled. Claims 2 and 4 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Specification

2. Applicant's response filed 4/7/03 placed the application in compliance with the sequence rules.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 4 are indefinite over the recitation of "having a "12" genotype" and "having a "11" genotype," respectively. The specification does not define these annotations to describe what a "11" genotype or a "12" genotype is, and thus, the method is unclear. The specification, at page 7 describes methods for the genotyping of the second exon of the myostatin

gene, but the specification does not describe how this method relates to the designations "11" and "12." Thus, it is impossible to ascertain what genotype is being identified in claims 2 and 4.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2 and 4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is drawn to a method of improving cholesterol levels in a subject in need of such improvement by identifying a subject with hypercholesteremia having a "12" genotype for a myostatin exon 2 gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

Claim 4 is drawn to a method for improving diabetes status in a subject by identifying a subject with diabetes having a "11" genotype for a myostatin exon 2 gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

As a first point, as noted in the rejections under 112 2nd paragraph, neither the specification nor the claims clearly set forth the meaning of the "11" or "12" genotypes, and thus, the methods of the instantly rejected claims are largely undefined. However, even if these

genotypes were clearly defined, the specification is not enabling for the practice of the claimed methods.

The claimed methods both rely on the establishment of a relationship between particular alleles in the second exon of the myostatin gene and a particular phenotype (i.e. the ability to improve cholesterol levels with extensive exercise or the ability to improve diabetes status with extensive exercise). The prior art is silent with respect to polymorphisms in the human myostatin gene. However, the state of the art with regard to the establishment of such a relationship between a polymorphism and a phenotype is highly unpredictable. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789).

The data in the specification highlight this unpredictability. With regard to methods for improving cholesterol status, the specification and claims assert that patients with a "12" genotype exhibit greater improvements after an extensive exercise routine for nine months. However, the data to support this assertion only represent three people total with the "12"

genotype and the standard deviations in the data points given are nearly as large as the average values reported. No statistical analysis is provided, so it is unknown from the data whether a statistically significant correlation was observed. Certainly the ranges of improvement observed for patients with the "12" genotype versus the "11" genotype overlap when the standard deviations are considered. Thus, the data themselves demonstrate that it is not predictable, even once a genotype is observed which patients will exhibit an improvement even after nine months of an extensive exercise regime.

The data regarding an improvement in diabetes status also is widely variant and represents a small sample population. Again, no statistical analysis is presented to aid in the interpretation of the data. In light of these factors it is impossible to ascertain whether a reliable association has been demonstrated between nine months of an extensive exercise regime and an improvement in diabetes status correlated with a particular phenotype.

Furthermore, it is noted that the claims encompass "extensive exercise" for any length of time, yet the specification provides only a demonstration of the changes that occur after nine months of endurance exercise training. It is highly unpredictable as to what other shorter lengths of training would be sufficient to improve cholesterol or diabetes status for patients having the "12" or "11" genotypes, as appropriate.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability, the lack of clearly defined and analyzed working examples, and the breadth of the claims, it is concluded that undue experimentation would be required to practice the claimed invention.

Response to Remarks

The 112 2nd rejection regarding the "12" and "11" genotypes is maintained. Applicant submits that the terms would be readily understood by one of ordinary skill in the art in view of a GENBANK record identifying human myostatin mRNA and teaching in the specification that states "Detection of a Lys153Arg Substitution in Myostatin Exon 2." However this is not persuasive. The GENBANK record does not discuss the polymorphism disclosed herein. The specification discloses a Lys153Arg substitution in myostatin exon 2, but does not assign what the designations "11" and "12" mean in terms of which particular variants of the myostatin are relevant to each designation. Applicant's remarks suggest that "11" is Lys at position 153 and "12" is Arg at position 153, but the designations could just as easily be the opposite, or "11" could mean one possible homozygote, "12" a heterozygote, and some other designation the other possible homozygote. Applicants have disclosed a new variant of the human myostatin gene and have failed to adequately define the nomenclature that they use to discuss the alleles present in samples. Furthermore, applicant suggests that in view of MPEP2154.05(a) the specification need not disclose what is well known to those skilled in the art. While this is true, it is not relevant in this instance, because the meanings of "11" and "12" relevant to the NOVEL polymorphism disclosed herein were not and could not have been known in the prior art since the polymorphism itself was not known in the prior art. While one may not need to disclose what is well known to those skilled in the art, one must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention, and in this case, applicant has failed to do so. The rejection is maintained.

With regard to the 112 1st rejection, applicant presents lengthy arguments to support the position that the Hacker and Pennisi references cited by the examiner are not relevant to the instant invention. While it is agreed that they are not art against the instant invention, these references were relied upon to demonstrate that within the field of genetic analysis, particularly the area in question where single nucleotide polymorphisms are being used as predictors of phenotypes, the state of the art is highly unpredictable. That is, there is no reliable or predictable way to know a priori if a particular polymorphism will be associated with any particular phenotype. Insofar as polymorphisms within the human myostatin gene were unknown at the time of the invention, the references were cited to establish the state of the art in general, which is highly unpredictable. Applicant's arguments have not rebutted this central point of the 112 1st paragraph rejection. Applicant's attempts to "overcome" the supplementary references do not address the rejection itself, which is based on a combination of a number of factors including the breadth of the claims, the level of unpredictability of the art, the lack of working examples, and the lack of clear direction provided in the specification which lead to the conclusion that undue experimentation would be required to practice the claimed invention.

With regard to the data presented in the specification, applicant states that the "data is sufficient for one of ordinary skill to determine the efficacy of the claimed methods." The claimed methods rely on an underlying relationship between the presence of particular phenotypes (i.e. an increased likelihood of positive response to extensive exercise) and a particular genotype. Applicants have not presented any data which supports such a relationship, the data presented by applicant is of such low power and significance that no conclusions can be made to support any relationship between a phenotype and a genotype. Applicants have

provided no evidence or argument to support the fact that the instant specification does demonstrate such a relationship. The specification and claims assert that for improving cholesterol status, patients with a "12" genotype exhibit greater improvements after an extensive exercise routine for nine months. However, the data to support this assertion only represent three people total with the "12" genotype and the standard deviations in the data points given are nearly as large as the average values reported. No statistical analysis is provided, so it is unknown from the data whether a statistically significant correlation was observed, but it is highly unlikely that any statistically significant correlation is observed given the lack of power and high level of variability in the data. Certainly the ranges of improvement observed for patients with the "12" genotype versus the "11" genotype overlap when the standard deviations are considered.

Finally, with regard to the comments regarding "extensive exercise" these comments are not merely a matter of opinion, but point out that the range of exercise encompassed within the claims is not commensurate in scope with the showings in the specification. There is no guidance given as to what levels of "extensive exercise" that are less than nine months of endurance training might work in the instant methods.

For all of these reasons, the rejections are maintained.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet Einsmann Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet Einsmann Switzer
Examiner
Art Unit 1634

June 18, 2003